REMARKS

Claims 61-81 are in this application, claims 1-60 having been cancelled and claims 61-61 having been added by this response. Claims 1-60 were rejected under 35 USC 101, 102, 103, and /or 112.

The amendment

Claims 1-60 were previously pending in this application; and all claims were rejected. Applicants have cancelled claims 1-60, without prejudice or disclaimer of the subject matter contained therein, and have added new claims 61-81, so that claims 61-81 are now pending. No new matter has been added. Support for claims 61-81 can be found in the application as noted below:

61: this is somewhat narrower than but equivalent generally to claim 51 of the application as originally filed when dependent on claim 43, but with the following changes:
(a) the active compound is now said to be either a diester of a compound of formula A (correcting an error in claim 43 – see claim 1 of the application as originally filed, which refers to a diester of a compound of formula A) or a pharmaceutically acceptable salt, or is a compound of formula I (which is already a diester) or a pharmaceutically acceptable salt;
(b) the lipids are now named as being egg phosphatidylcholine (EPC) and egg phosphatidylglycerol (EPG) in a ratio of 0.75-1.25:0.75-1.25 by weight (using the preferred ratio of claim 51 – all ratios in the application are weight ratios).

62: the compound (as the dihydrochloride salt) is compound 9 on page 23 of the application.

63: the lipid/compound range is the broader range of claim 46 of the application as filed, 3.5-4.5:0.5-1.5 represents a ratio of 2.33:1-9:1 (3.5:1.5 is 2.33:1 and 4.5:0.5 is 9:1).

64: the range is the narrow range of claim 46 of the application as filed.

65: a liposomal formulation is seen at page 5, lines 1-2 and 22-28 of the application as filed.

66: this is based on claim 44; the EPC and EPG are naturally occurring lipids, and the liposomal charge features of the claim are listed in separate sentences at page 10, lines 21-22 of the application as filed, so the presence of a net negative charge is independent of the other features.

67: the encapsulation range is the preferred range of claim 45 of the application as filed.

68: the vesicle size is the preferred range of claim 47 of the application as filed.

69: composition from claim 52 of the application as filed.

70: compound 9 on page 23 in composition of claim 52.

71: lyophilization of the liposomes is seen at page 10, lines 28-29 and page 15, lines 5-6.
See also Examples 4-9 (pages 25-29) for examples of liposomal formulations of compound 9.

72: the formulation is that of new claim 61, and the method is discussed generally in the application at page 14, line 15 to page 15, line 6 (lipid emulsions and liposomes).

73: compound 9 on page 23.

74: liposomal formulation seen at page 5, lines 1-2 and 22-28.

75: use of extrusion to prepare liposomes at page 15, lines 4-5.

76: lyophilization at page 15, lines 5-6.

77: formulation of new claim 70, method described at Example 4, starting on page 25.

78: as in claim 77 and includes lyophilization of the prepared liposomes.

79: product-by-process claim based on the method of claim 77.

80: product-by-process claim based on the method of claim 78.

81: the method for the modulation of hematopoiesis and protection against destructive effects of chemotherapy is seen at page 5, lines 29-37 and in claims such as claim 53 as filed. The claim is dependent, in the alternative, on each of the formulation claims (60-71, 79, and 80).

Applicants will sequentially address the issues raised in the Office Action, with the paragraphs of this response numbered as in the Office Action.

Rejection under 35 U.S.C. §101 and §112

1. Claims 42 and 60 stand rejected under 35 U.S.C. §101 and §112 as providing for the use of the compounds but without describing process steps.

Applicants have cancelled claims 42 and 60, and the new claims 61-81 do not contain the objected-to "use" language. Applicants respectfully submit that new claims 61-81 are directed to statutory subject matter.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §101 and §112 as those rejections may be applied to new claims 61-81.

Rejections under 35 U.S.C. §102(b)

3. Claims 1-4, 7-15, 18-24, 27-35, and 38-42 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kauvar et al. (US Patent No. 5,955,432) or PCT Publication No. WO 96/40205. The Office Action states that both Kauvar et al. and WO 96/40205 "disclose a method of stimulating hematopoiesis using the same claimed compounds."

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 1-4, 7-15, 18-24, 27-35, and 38-42. As explained above in discussing the support for new claims 61-81, the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), which was not rejected for anticipation, and the broadest method and process of manufacturing claims are of the same formulation scope. Applicants respectfully submit that new claims 61-81 are not anticipated by either of the cited references, neither of which disclose the claimed lipid formulations.

4. Claims 21-24, 27-35, and 38-42 stand rejected under 35 U.S.C. §102(b) as being anticipated by Morgan et al. (*Cancer Chemother. Pharmacol.*, 37, 363-370 (1996)). The Office Action states that Morgan et al. "disclose a method of administration of the claimed compounds to potentiate the effect of therapeutic compounds."

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 21-24, 27-35, and 38-42. As explained above in discussing the support for new claims 61-81, the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), which was not rejected for anticipation, and the broadest method and process of manufacturing claims are of the same formulation scope. Applicants respectfully submit that new claims 61-81 are not anticipated by the cited reference, which does not disclose the claimed lipid formulations.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102(b) as those rejections may be applied to new claims 61-81.

Rejections under 35 U.S.C. §103(a)

6. Claims 5-6, 16-17, 25-26, 36-37, and 43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kauvar et al. or WO 96/40205. The Office Action states that both Kauvar et al. and WO 96/40205 "disclose a method of stimulating hematopoiesis using the same claimed compounds" and that although they "do not show the administration of the compounds in liposomal form, through examples, both suggest the use of liposomes for the delivery of the compounds."

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 5-6, 16-17, 25-26, 36-37, and 43. As explained above in discussing the support for new claims 61-81, the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), which was not rejected as unpatentable over the cited references, and the broadest method and process of manufacturing claims are of the same formulation scope. Applicants respectfully submit that new claims 61-81 are not unpatentable over either of the cited references, neither of which disclose or suggest the claimed lipid formulations.

7. Claims 5-6, 16-17, 25-26, 36-37, and 43-60 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kauvar et al. or WO 96/40205, further in view of Yau-Young (US Patent No. 5,023,087), Barenholz et al. (US Patent No. 5,043,166), Straubinger et al. (US Patent No. 5,415,869), or Lambiez et al. (US Patent No. 5,605,703), alone or in combination. The Office Action states that both Kauvar et al. and WO 96/40205 "are suggestive of the use of liposomes for the delivery of the claimed compounds. What are lacking in the references however, are the teachings of the use of specific liposomes, that is, negatively charged." The Office Action then refers to Yau-Young as disclosing liposomal formulations for increased stability, in which the liposomes are made from egg PC and PG; Barenholz et al. as teaching that negatively charged phospholipids such as PG and PS tend to enhance liposome stability, Straubinger et al. as disclosing liposomal Taxol formulations and teaching that liposomes containing PC and PG are physically stable, and Lambiez et al. as disclosing doxorubicin-containing liposomes and teaching that the use of a negatively charged phospholipids favors stability of the liposome solution.

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 5-6, 16-17, 25-26, 36-37, and 43-50, while the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), and the broadest method and process of manufacturing claims are of the same formulation scope.

With regard to the primary references, it is accepted that neither Kauvar et al. nor WO 96/40205 anticipate or render unpatentable claims 61-81, because these new claims are narrower than claims that were not considered to be anticipated or unpatentable in the prior claim set (see the discussions in paragraphs **3** and **6** above), and indeed the Office Action notes that the references "are lacking the teachings of the use of specific liposomes".

The Office Action points to Yau-Young as showing liposomal formulations made from egg PC and PG, referring to the Abstract; col. 7, l. 58 – col. 8, l. 18; col. 9, l. 65 – col. 10, l. 49; col. 16, l. 34 et seq., col. 18, l. 45 et seq. and the Examples. It is accepted that Yau-Young discloses egg PC (EPC), soy PC, and egg PG (EPG) as preferred PC and PGs (col. 7, ll. 52-53). However, taking each location in turn: the Abstract does not disclose any liposome-forming materials or ratios; col. 7, l. 58 – col. 8, l. 18, while disclosing that negatively charged phospholipids increase the rate of clearance, discloses no lipid ratios; col. 9, l. 65 – col. 10, l. 49, while disclosing the advantage of liposomal compositions, does not disclose any liposome-forming materials or ratios; col. 16, l. 34 et

seq., while also disclosing the advantage of liposomal compositions, does not disclose any liposome-forming materials or ratios; and col. 18, l. 45 et seq., while disclosing uses for liposomal compositions, does not disclose any liposome-forming materials or ratios. Looking then to the Examples, Example 1 shows five lipid formulations of which three containing one or more of EPC and EPG and no other lipid, but they have EPC:EPG ratios of ∞ (EPC but no EPG) in composition A, 18.8:1 in B, and 0 (EPG but no EPC) in D: all well outside the 0.75:1.25-1.25:0.75 range claimed in claim 61. No later Example shows any formulation having different lipid ratios. Applicants respectfully submit that while Yau-Young does indeed show EPC:EPG liposomes, Yau-Young neither discloses nor suggests the EPC:EPG ratio claimed in claim 61, and thus fails to remedy the deficiency of the primary references.

The Office Action points to Barenholz et al. as teaching that negatively charged phospholipids such as PG and PS tend to enhance stability, referring to col. 6, l. 57 et seq., Tables III and IV, and the Example. It is accepted that Barenholz et al. at col. 6, l. 57 et seq. state that negatively charged phospholipids such as PG and PS tend to enhance drug liposome stability in liposomal doxorubicin, but give no lipid ratios. And, taking each remaining location in turn: Table III shows 12 formulations, of which only one contains both PC and PG and no other lipid, and that is in a ratio of 7:3; Table IV also shows 12 formulations, of which none contain only PC and PG and no other lipids; and Example I shows a formulation which, while containing EPC and EPG, also contains cholesterol, and is therefore outside the scope of the new claims. An EPC:EPG ratio of 7:3 (2.33:1) is well outside the 0.75:1.25-1.25:0.75 range claimed in claim 61. Applicants respectfully submit that while Barenholz et al. does indeed show EPC:EPG-containing liposomes, it neither discloses nor suggests the EPC:EPG ratio claimed in claim 61, and thus fails to remedy the deficiency of the primary references.

The Office Action points to Straubinger et al. while disclosing liposomal Taxol formulations as teaching that liposomes containing PG and PC are stable and retain Taxol content, referring to Example 2. However, the formulation of Example 2 contains PC and PG (and not specifically EPC and EPG as claimed) at a 9:1 ratio, well outside the 0.75:1.25-1.25:0.75 range claimed in claim 61. Applicants respectfully submit that while Straubinger et al. does indeed show PC:PG-containing liposomes for Taxol, it neither discloses nor suggests the EPC:EPG ratio claimed in claim 61, and thus fails to remedy the deficiency of the primary references.

Finally, the Office Action points to Lambiez et al. "while disclosing doxorubicin-containing liposomes teaches that the inclusion of a negatively charged phospholipid favors the stability of the liposome solution", referring to the Abstract, col. 4, l. 24 et seq., Table II, and the claims. It is accepted that Lambiez et al. teaches the inclusion of a negatively charged phospholipid in liposomes for the encapsulation of doxorubicin. However, the Abstract discloses no liposome-forming materials or ratios, and col. 4, l. 24 et seq. gives only broad guidance , while Example 2 shows 11 formulations of three types, in which the formulation containing PC and PG also contains cholesterol in a ratio PC:PG:cholesterol of 1:1:1. There is no liposomal formulation containing only PC and PG as the lipids. Applicants respectfully submit that while Lambiez et al. does indeed show doxorubicin-containing liposomes, it neither discloses nor suggests the formulation claimed in claim 61 (and hence the dependent claims), and thus fails to remedy the deficiency of the primary references.

Thus none of the secondary references individually, and hence none of the secondary references in combination, discloses the use of EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 by weight as the sole lipids in the formulation, and therefore they each, individually and collectively, fail to remedy the deficiencies of the primary references.

Preparations containing 100% EPC or a high EPC/EPG ratio, such as 9:1, are common in the preparation of liposomes, as may be seen from the art cited in the Office Action and also in the following three references:
Z. Pavelic et al., "Development and in vitro evaluation of a liposomal vaginal delivery system for acyclovir", Poster Abstract; 1 April 2003; obtained from http://www.dekker.com/servlet/-product/DOI/101081LPR120017490/section/abstract_38 (disclosing formulations with EPC alone and EPC/EPG in a 9:1 ratio),
R.J.H. Stenekes et al., "Degradable dextran microspheres for the controlled release of liposomes", *Int. J. Pharmaceutics*, **214**, 17-20 (2001) (disclosing a formulation with EPC/EPG in a 9:1 ratio, either alone or microencapsulated), and
D. Reimer et al., "Cyclosporin (CSA) release from microemulsion: effect of membrane apposition", CSPS 5th Symposium on Pharmaceutical Sciences '02, *J. Pharm. Pharmaceut. Sci.* (www.ualberta.ca/ ~csps), 5(2), 39-122 (2002) (disclosing a formulation with EPC/EPG in a 9:1 ratio).

However, none of these disclose or suggest formulations containing EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 as the sole lipids to formulate compounds of formula A or I as shown in new claim 61.

Applicants respectfully submit that, because the primary references "are lacking the teachings of the use of specific liposomes" (Office Action) and because the secondary references, by themselves or in combination, fail to disclose or suggest formulations containing EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 as the sole lipids to formulate compounds of formula A or I as shown in new claim 61, new claims 61-81 are not unpatentable over the cited references, which do not disclose or suggest the claimed formulations.

8. Claims 25-26, 36-37, 43-52, and 57 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Morgan et al., further in view of Yau-Young (US Patent No. 5,023,087), Barenholz et al. (US Patent No. 5,043,166), Straubinger et al. (US Patent No. 5,415,869), or Lambiez et al. (US Patent No. 5,605,703), alone or in combination. The Office Action states that "the teachings of Morgan et al. have been discussed above. What are lacking in Morgan et al are the teachings of the use of liposomes for the delivery of the compounds" and provides the same discussion with respect to Yau-Young, Barenholz et al., Straubinger et al., and Lambiez et al. as provided in the discussion of the rejection over Kauvar et al. and WO 96/40205 in view of these same secondary references.

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 5-6, 16-17, 25-26, 36-37, and 43-50, while the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), and the broadest method and process of manufacturing claims are of the same formulation scope.

With regard to the primary references, it is accepted that Morgan et al. does not anticipate or render unpatentable claims 61-81, because these new claims are narrower than claims that were not considered to be anticipated or unpatentable in the prior claim set (see the discussions in paragraph 4 above and no rejection for obviousness was made), and indeed the Office Action notes that the reference is lacking "the teachings of the use of liposomes for the delivery of the compounds".

As discussed in the response to the rejection under 35 USC 103(a) over Kauvar et al. or WO 96/40205, further in view of Yau-Young, Barenholz et al., Straubinger et al., or Lambiez et al., alone or in combination (paragraph 7 above), none of the secondary references individually, and hence none of the secondary references in combination, discloses the use of EPC and EPG in a

ratio of 0.75-1.25:0.75-1.25 by weight as the sole lipids in the formulation, and therefore they each, individually and collectively, fail to remedy the deficiencies of the primary references.

Applicants respectfully submit that, because the primary reference is "the teachings of the use of liposomes for the delivery of the compounds" (Office Action) and because the secondary references, by themselves or in combination, fail to disclose or suggest formulations containing EPC and EPG in a ratio of 0.75-1.25:0.75-1.25 as the sole lipids to formulate compounds of formula A or I as shown in new claim 61, new claims 61-81 are not unpatentable over the cited references, which do not disclose or suggest the claimed formulations.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103(a) as those rejections may be applied to new claims 61-81.

Double patenting rejections

10. Claims 1-43 stand rejected for obvious-type double patenting over claims 1-38 of Kauvar et al. The Office Action states that the conflicting claims are not patentably distinct because they "are drawn to the same compounds and method of stimulating hematopoiesis or method of potentiating a chemotherapeutic compound effect" and that although the patent claims "do not recite lipid formulations, in view of the language 'comprising' in the claims and reciting of pharmaceutically acceptable excipients, these claims are included in the rejection."

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 1-43 because the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), which was not rejected for double patenting, and the method and process of manufacturing claims are of the same formulation scope. Applicants respectfully submit that new claims 61-81 are not double-patented over claims 1-38 of Kauvar et al., which does not disclose or suggest the claimed lipid formulations.

11. Claims 5-6, 16-17, 25-26, 37-37, and 43-60 stand rejected for obvious-type double patenting over claims 1-38 of Kauvar et al. in view of Yau-Young, Barenholz et al., Straubinger et al., or Lambiez et al., alone or in combination. The Office Action states that the "the claims in said patent do not recite lipid carrier or specifically negatively charged liposomes as carriers. The patent in the specification however, recites liposomes as carriers." The Examiner then provides the same discussion with respect to Yau-Young, Barenholz et al., Straubinger et al., and Lambiez et al. as provided in the discussion of the rejection of the same claims for obviousness over Kauvar et al. and WO 96/40205 in view of these same secondary references, and concludes that "The use of liposomes, negatively charged liposomes for the delivery of the compounds in US 5,955,432 would have been obvious to one of ordinary skill in the art because of the advantages taught by" the secondary references.

Applicants have cancelled claims 1-60, and replaced them with new claims 61-81. Applicants respectfully submit that new claims 61-81 are not double-patented over claims 1-38 of Kauvar et al. in view of Yau-Young, Barenholz et al., Straubinger et al., or Lambiez et al., alone or in combination, for the reasons given in paragraph 7. above responding to a rejection for obviousness of the same claims over the entire disclosure of Kauvar et al. in view of the same combination of secondary references.

12. Claims 29-35 and 38-41 stand rejected for obvious-type double patenting over claims 1-18 of US Patent No. 5,679,643. The Office Action states that the conflicting claims are not patentably distinct because they "are drawn to the same compounds. Instant claims recite 'pharmaceutical compositions' and there is no patentable distinction between compound claims and composition claims."

Applicants have cancelled claims 1-60, and note that new claims 61-81 are not equivalent to any of claims 29-35 and 38-41 because the broadest formulation claim now presented, claim 61, is somewhat narrower than but equivalent generally to prior claim 51 (as dependent on claim 43), which was not rejected for double patenting, and the method and process of manufacturing claims are of the same formulation scope. Applicants respectfully submit that new claims 61-81 are not double-patented over claims 1-18 of US Patent No. 5,679,643, which does not disclose the claimed lipid formulations.

Applicants respectfully request withdrawal of the double patenting rejections as those rejections may be applied to new claims 61-81.

Information Disclosure

Applicants direct the attention of the Office to the documents listed on the attached Form PTO-1449 substitute, that may be relevant to the examination of this application.

Applicants believe that the Office is well aware of WO 00/44366, cited as document 1A, as the International Search Report from it was provided with the IDS filed in January 2002 As will be apparent, WO 00/44366 has the same inventorship and disclosure as this application (this application was filed using the text of WO 00/44366 as filed), and was published less than one year before the filing date of this application (3 August 2000 and 10 July 2001).

The three non-patent publications cited as documents 2A – 4A are discussed in the response above (at page 10).

The Examiner is requested to initial and return a copy of the form with the next communication on this application.

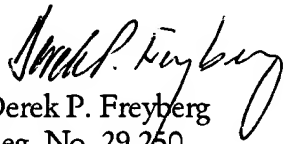
No representation is made by this Information Disclosure Statement that a search has been made; or that the information disclosed is, or is considered to be, material to patentability under 37 CFR 1.56(b).

Conclusion

Applicants submit that new claims 61-81 are fully supported by the application as filed and define patentable subject matter. Re-examination and allowance of claims 61-81 are respectfully requested.

Applicants reserve the right to file divisional and/or continuation application(s) to the subject matter canceled in this and previous responses.

Respectfully submitted,



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